PATENT
Customer No. 22,852
Attorney Docket No. 06478.1452-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Hubert METZNER et al.	)	Group Art Unit: 1654
	)	
Application No.: 09/809,021	)	Examiner: Michael V. Meller
	)	
Filed: March 16, 2001	)	
	)	
For: THROMBIN PREPARATIONS AND PROCESS FOR THEIR PRODUCTION	)	

Mail Stop Appeal Brief--Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

In support of the Notice of Appeal filed March 1, 2004, and pursuant to 37 C.F.R. § 1.192, Appellants present an original and two copies of their brief and a check in the amount of $110.00 for the one month extension fee under 37 C.F.R. § 1.17(c) and the fee in the amount of $330.00 for the Appeal Brief.

The period of response is extended to June 1, 2004, by the Petition for Extension of Time and accompanying fee filed herewith. Please grant any extensions of time necessary to enter this Appeal Brief. Further, if there are any fees required to enter this Appeal Brief that are not otherwise accounted for, please charge such fees to Deposit Account 06-0916.

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I. Real Party In Interest

The real party of interest is ZLB Behring GmbH, formerly known as Aventis Behring GmbH. The assignment to Aventis Behring GmbH was recorded on September 16, 2001, at Reel 011624, Frame 0455.

II. Related Appeals and Interferences

The Appellants, undersigned, and assignee are not aware of any other appeals or interferences that will directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. Status Of Claims

Claims 1-17 were originally filed in this application. All of these claims were canceled in the Preliminary Amendment filed on March 16, 2001, and their subject matter was re-submitted in claims 18-34.

The Office withdrew claims 20-34 in a restriction requirement mailed November 23, 2001. Therefore, only claims 18-19 and 35-38 are under examination and are shown in the Appendix herein. Applicants traversed the restriction requirement in the Amendment filed April 23, 2002, and requested rejoinder of the withdrawn claims, once the Office considers claims 18-19 and 35-38 allowable. (See page 3 of the Amendment filed April 23, 2002.)

Claims 18 was amended and claims 35-38 added in the Amendment filed April 23, 2002. Claim 19 was amended in the Amendment filed November 19, 2002.

IV. Status Of Amendments

All amendments have been entered.

V. Summary Of Invention

The instant invention, as recited in claim 18, is a preparation that comprises thrombin protein and a noncovalently binding inhibitor of thrombin activity. The claimed preparation containing these two ingredients is also "suitable for therapeutic purposes," meaning that it is safe for direct administration to a patient, for example. The thrombin preparation may be used, for example, as a component of a tissue glue, or as a local hemostatic agent. (Specification at page 1, second paragraph.) Claim 18, like all of the other pending claims, is supported by the application as a whole. Particular support may be found, for example, in original claim 1 in the first paragraph of the text at page 1, and in the first full paragraph on page 6.

The other claims under appeal depend from claim 18. Claim 19 recites that the thrombin preparation also comprises a soluble calcium salt, sodium chloride as a stabilizer, a buffer substance, and at least one of a sugar, sugar alcohol, amino acid, a mono- or polycarboxylic acid salt, or a mono- or polyhydroxycarboxylic acid salt. The thrombin preparation of claim 19 is also stable in the liquid state. This claim is supported, *inter alia*, in original claim 2, and at the paragraph bridging pages 5 and 6.

Claims 35 and 36 recite that the noncovalently binding inhibitor of thrombin activity is either benzamidine (claim 35) or p-aminobenzamidine (claim 36). These claims are supported, for example, at the first full paragraph of page 6 and the paragraph bridging pages 6 and 7.

Claim 37 recites that the thrombin protein within the claimed preparation maintains at least 70% of its original level of activity after 12 months of storage at 20-25 °C. This claim is supported, for example, at the second full paragraph on page 6 and at

the paragraph bridging pages 6 and 7. Further, Tables 4 and 5 at pages 12-15 present data showing that two thrombin preparations as claimed (numbers 8 and 9) retain about 80-90% of the original thrombin activity after 12 months of storage at 20-25 °C, while other preparations retain only about 40-65% of the original thrombin activity under these conditions.

Claim 38 recites that the claimed thrombin preparation has a pH of 5.0 to 8.0. This claim is supported, for example, at the paragraph bridging pages 5 and 6.

Because withdrawn claims 20-34 are not part of the instant appeal, they are not discussed in detail in this section and are not presented in the Appendix. These claims recite methods of making and using thrombin preparations.

VI. Issues

1. Whether claims 18-19 and 35-38 are enabled under 35 U.S.C. § 112, first paragraph.
2. Whether claims 18 and 35-38 are anticipated under 35 U.S.C. § 102(b) by Hanada et al.
3. Whether claims 18, 35, and 37 are anticipated under 35 U.S.C. § 102(b) by the abstract of either Allary et al. or Lorne et al.
4. Whether claim 38 is obvious under 35 U.S.C. § 103(a) over Hanada et al.
5. Whether claims 18-19 and 35-38 are obvious under 35 U.S.C. § 103(a) over Hanada et al., taken with Brezniak et al. and Altshuler.
6. Whether claims 18-19 and 35-38 are obvious under 35 U.S.C. § 103(a) over (a) the abstract of Allary et al. or Lorne et al., taken with Hanada et al.,

Brezniak et al., and Altshuler, or over (b) Hanada et al., taken with the abstract of Allary et al. or Lorne et al., and further with Brezniak et al. and Altshuler.

VII. Grouping Of Claims

For the purposes of this appeal, claims 18-19 and 35-38 stand or fall together.

VIII. Argument

1. Claims 18-19 and 35-38 Are Enabled

The Examiner rejects claims 18-19 and 35-38 under 35 U.S.C. § 112, asserting that they are not enabled throughout their full scope. (Final Office Action of November 28, 2003, (hereinafter "Final Office Action") at pages 2-3.) The Examiner first contends that the particular noncovalently binding inhibitors of thrombin activity recited in claims 35 and 36 are enabled, but that other noncovalently binding inhibitors of thrombin activity are not enabled. (*Id.* at page 2.) Second, the Examiner acknowledges that specific examples of the additives of claim 19 tested in the application are enabled, such as the amino acids L-histidine, L-arginine, the carboxylic acid salt succinate, and the sugar alcohol mannitol. But the Examiner asserts that amino acids, sugars, sugar alcohols, carboxylic acid salts, or hydroxycarboxylic acid salts not specifically tested in the application are not enabled. (Final Office Action at pages 2-3.) This rejection is not a *prima facie* case.

First, it is the Examiner who bears the initial burden to set forth a *prima facie* case of unpatentability. A patent application's teachings must be taken as enabling the claims, unless there is reason to doubt the objective truth of those teachings. *In re*

Marzocchi, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Therefore, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning." *Id.* at 224, 169 U.S.P.Q. at 370. Indeed, appropriate evidence or reasoning is necessary to satisfy the substantial evidence standard of *In re Zurko*, 258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001).

Second, the relevant question in an enablement rejection is not the type or amount of experimentation that might be needed to make or use a claimed invention, but whether that experimentation is "undue." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Determining whether or not the level of experimentation is "undue" involves analyzing the necessary experimentation in light of several factors, such as the nature of the invention, the scope of the claims, the predictability of the invention, the level of ordinary skill in the art, the state or maturity of the art, and the guidance available from both the application and prior art. *See Id.*, *and see* M.P.E.P. § 2164.01(a). Further, the enablement standard allows for a considerable amount of experimentation, if that experimentation is routine or is sufficiently guided by the art. *Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404, (citing *In re Angstadt*, 537 F.2d 489, 502-4, 190 U.S.P.Q. 214, 217-9 (C.C.P.A. 1976)).

The M.P.E.P. also counsels that a composition to be used pharmaceutically does not need to satisfy a high level of utility, such as that required in Food and Drug Administration clinical trials. M.P.E.P. § 2107.01(III). As the Federal Circuit explained in In re Brana, "[w]ere we to require Phase II testing in order to prove utility, the

associated costs would prevent many companies from obtaining patent protection. . ." 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Thus, a therapeutically useful composition need only have credible pharmaceutical utility, and its enablement should be judged according to that level of activity.

Here, the Examiner appears to question whether the therapeutic suitability of the claimed thrombin preparations is predictable. Yet the Examiner sets forth only a series of generic statements, rather than evidence or reasoning focusing upon the instant claims and on the undue experimentation standard. For example, the Examiner repeatedly asserts that "biotechnology is a highly unpredictable art," and therefore contends that "it would be an undue burden for one of ordinary skill in the art to test any and all inhibitors of thrombin, sugars, sugar alcohols, amino acids, etc." for the disclosed uses. (Final Office Action at page 3, first three lines; and see the Office Action of May 6, 2003, at page 3.) In addition, the Examiner contends that "[t]he art of biotechnology is highly unpredictable and to know which noncovalently binding inhibitor of thrombin activity could be just about anything" and that "it is not even clear how one would even go about trying to figure out what substances even fall within this category." (Final Office Action at page 3, final paragraph.) Statements about the predictability of biotechnology in general do not satisfy the substantial evidence standard of *Zurko* or the burden under *Marzocchi*. Nor do unreasoned conclusory statements such as those above. In addition, the Examiner does not consider the other factors from *Wands* that weigh in favor of enablement, such as the guidance in the application and prior art, the state of the art, and the level of ordinary skill in the art. For all of these reasons, the Examiner's contentions do not establish a *prima facie* case of non-enablement.

When the Examiner does not meet his initial burden to set forth a *prima facie* case, Appellants are not required to submit any evidence or reasoning to rebut the Examiner's assertions. Nevertheless, Appellants previously provided the Examiner with ample evidence demonstrating that the invention is well guided by the application and the prior art and that the state of the art of thrombin preparations is relatively mature. (See Appellants' Remarks filed September 8, 2003, at pages 8-11, for example.)

First, the Examiner contends that the claims are not enabled beyond the specific noncovalently binding inhibitors of thrombin activity recited in claims 35 and 36 - benzamidine and p-aminobenzamidine. He also contends that the scope of this class of inhibitors is unclear. Yet the specification guides those of ordinary skill in the art to other appropriate "noncovalently binding inhibitors of thrombin activity" and explains how to test whether a given compound falls within this class. These compounds are low to moderate affinity protease inhibitors that do not significantly decrease the activity of thrombin in relation to fibrinogen in a coagulation test. (See the specification at page 6, first full paragraph, to page 7, line 4; the coagulation test is described below.) The prior art provides additional guidance. For example, thrombin is a serine protease that uses an arginine or lysine in its active site. Therefore, noncovalently binding inhibitors of thrombin activity include those that mimic arginine or lysine, such as arginine-derived or benzamidine-based inhibitors. (Specification at page 6, first full paragraph.) Appellants also provided the Examiner with an article that lists several such inhibitors. (See Stürzebecher et al., page 496, final paragraph.)

In addition, several noncovalent thrombin inhibitors that could be administered to patients separately, in the absence of thrombin, were known before this application was

filed. For example, an article by Hauptmann references clinical trials on a small set of therapeutically suitable thrombin inhibitors administered alone. (See Hauptmann at page 752, column 2, discussing the benzamidine-based inhibitor NAPAP and others, citing publications describing the development and clinical testing of these inhibitors prior to Applicants' filing date.) Thus, one of ordinary skill in the art could reasonably predict that separate solutions of such noncovalently binding thrombin inhibitors are therapeutically safe.

The Examiner also contends that the optional components of the solution recited in claim 19 (e.g. sugars, amino acids, sugar alcohols, and salts of carboxylic acids or hydrocarboxylic acids) are not enabled throughout their full scope. However, Appellants previously demonstrated that these are common additives to therapeutic blood protein solutions. For example, they are frequently added simply as preservatives to enhance the shelf-life of the overall protein composition, or to protect the protein from exposure to high temperatures. (See the Specification at page 1, final paragraph, to page 2, end of third full paragraph.)

Appellants previously submitted four United States patents that disclose the use of salt, amino acid, sugar, and sugar alcohol additives in therapeutic blood protein preparations. U.S. Patent No. 4,297,344, for example, discloses that amino acids, sugars, and sugar alcohols are generally useful preservatives added to blood protein solutions, for example to enhance their stability to heat. The patent gives many examples of amino acids, sugars, and sugar alcohols that can be used with a variety of blood proteins. (See col. 3, lines 45-50, and the further discussion at col. 4.) U.S. Patents 4,579,735, 4,623,717, and 4,876,241 contain similar disclosures. All four of

these patents show that those in the art believe these classes of compounds to be generally useful additives, and also show that many different species within those classes are routinely used in protein solutions. Moreover, the Examiner does not present any evidence or reasoning to suggest that any of these agents would detract from the usefulness or therapeutic suitability of the instant, claimed preparations, or that they would change the key properties of the claimed preparations in any way.

The articles and patents referenced above show that the art of preparing liquid protein solutions is relatively mature and that those in the art are familiar with the sugar, sugar alcohol, amino acid, and carboxylic acid additives recited in claim 19. The articles provided herewith also show that the available class of "noncovalently binding inhibitors of thrombin activity" is relatively small and that it includes compounds that are known to be "suitable for therapeutic purposes" in themselves.

In addition, the coagulation tests used to choose an appropriate type and concentration of inhibitor or other additive are simple, routine procedures that involve determining how long it takes the thrombin preparation to cause a blood sample to coagulate. A variety of such screens are commercially available and they are routinely carried out by laboratory technicians. For example, the specification at the bottom of page 11 notes that the stability of several example formulations was tested by "determining the thrombin activity in a coagulation test with fibrinogen as substrate." (Application at page 11, final three lines.) Boctor et al., of record, gives an example of such a test, developed at the National Institutes of Health. (U.S. Patent No. 5,397,704, at col. 3, line 51, to col. 4, line 23.) In that assay, the thrombin solution is added to a solution of human plasma. The clotting time is measured with a commercial fibrometer

instrument and compared to a standard. The supplementary material of Landis et al., also of record, describes a similar clotting activity assay. (B.H. Landis et al., *J. Biol. Chem.* 256(9): 4604-10 (1981), at page 4608.) Such a simple assay of clotting versus time on a commercial instrument is a routine laboratory procedure that requires no undue experimentation.

Further, to determine if the thrombin is sufficiently active after 12 months of storage according to claim 37, one can perform a coagulation test as above before and after that storage and simply compare the results. A straightforward animal toxicity or clearance screen against a control thrombin preparation may verify that a solution is sufficiently safe to be therapeutically suitable as claimed. Finally, while the claimed preparations must be "therapeutically suitable" such that they can be directly administered to a patient, they do not have to meet detailed Food and Drug Administration efficacy standards in order to be patentable.

Still further, even if this art is unpredictable as the Examiner contends, Appellants are entitled to claims that are directed to their broader disclosure so as to provide the level of protection that is commensurate with their invention. As the court stated in *In re Angstadt*:

> Appellants have apparently not disclosed ***every*** catalyst which will work; they have apparently not disclosed ***every*** catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with ***every*** species covered by the claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent

> applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed.

190 U.S.P.Q. at 218 (emphasis in original) (footnote omitted). As in *Angstadt*, Appellants application and the prior art provides ample guidance for one of ordinary skill to make and use Appellants' claimed compositions without undue experimentation.

In summary, the Examiner does not present a *prima facie* case of non-enablement because he does not present sufficient evidence or reasoning directed at the instant claims and because he does not consider factors other than the predictability and scope of the claims. When these other factors are considered, it is clear that it requires no undue experimentation to make and use Appellants' claimed invention. Accordingly, Appellants respectfully request the Board to overturn this rejection.

2. Rejection of Claims 18 and 35-37 under 35 U.S.C. § 102(b): Hanada et al.

The Examiner asserts that claims 18 and 35-37 are anticipated by Hanada et al. ("Hanada"; U.S. Patent No. 5,945,103). (Final Office Action at pages 4-5.) The Examiner also contends that claim 38 is either anticipated by Hanada et al., or, in the alternative, obvious over Hanada. (Final Office Action at pages 5-6; the obviousness rejection is discussed in part 4 below.) As Appellants explain below, the Examiner does not properly analyze Hanada's teachings against the limitations of claim 18. Thus, these rejections are not *prima facie* cases of anticipation.

Anticipation is only established if a single reference expressly or inherently teaches every limitation of the claim, including all functional limitations. *See, e.g., Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); M.P.E.P. § 2131. Further, "[t]he elements must be arranged as

required by the claim." M.P.E.P. § 2131 (citing *In re Bond*, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

Here, the "thrombin preparation" of claim 18 comprises two ingredients: "thrombin" and a "noncovalently binding inhibitor of thrombin activity." Claim 18 also contains a functional limitation "wherein the thrombin preparation," meaning the entire claimed preparation comprising both ingredients, "is suitable for therapeutic purposes." Thus, claim 18 does not cover every solution containing both thrombin and a "noncovalently binding inhibitor of thrombin activity," but only a subset of such solutions that are "suitable for therapeutic purposes," meaning that they are safe for direct and immediate administration to a patient.

Hanada's solutions do not satisfy the limitations of claim 18. First, Hanada teaches how to prepare a solution of pure thrombin. For example, Hanada's general process involves the "purification of prothrombin," followed by "conversion of prothrombin to thrombin," then "purification of thrombin." (Hanada at col. 1, lines 27-31.) This process is exemplified in Example 1 at col. 5. That example shows the preparation of "purified thrombin," with no mention of any other final ingredient beyond simple buffer components such as sodium citrate. (See Hanada at col. 5, lines 31-50, for example.) That pure thrombin solution cannot anticipate claim 18 because it does not contain any "noncovalently binding inhibitor of thrombin activity."

The Examiner contends, nevertheless, that Hanada teaches using a "noncovalently binding inhibitor of thrombin activity." That contention is based on an optional intermediate step in Hanada's process, described at col. 4, lines 12-37, and illustrated in Example 1, at col. 5, lines 26-50. That intermediate treatment is

performed before the thrombin is purified and is designed to kill viruses, using compounds called trialkylphosphates to disrupt viral membranes. During this trialkylphosphate treatment, Hanada notes that benzamidine, a thrombin inhibitor, may be added to the solution. (Hanada at col. 4, lines 20-28.)

The only way in which Hanada could, *arguendo*, anticipate claim 18 is if its intermediate solution was inherently and necessarily "suitable for therapeutic purposes." But Appellants have demonstrated on record that it is not.[1] For example, Appellants presented evidence that trialkylphosphates disrupt biological membranes, are skin irritants, and are potentially harmful to human tissues. (See Exhibits A-C of the Amendment filed November 19, 2002, resubmitted herewith, and page 6 of that Amendment.) Further, Hanada itself teaches that the ingredients from the trialkylphosphate step should be removed before a purified thrombin solution is made by running the intermediate through an SP-SEPHADEX® C-50 column, thus "effecting adsorption of thrombin alone." (Col. 5, lines 26-37.) In other words, Hanada et al. did not consider the intermediate to be "suitable for therapeutic purposes."

Thus, comparing Hanada to the limitations of claim 18 shows that Hanada does not teach any composition comprising both "thrombin" and a "noncovalently binding inhibitor of thrombin activity" that is also "suitable for therapeutic purposes." Thus, Hanada cannot anticipate claim 18 or any of its dependents.

Despite reviewing this evidence, the Examiner insists that Hanada anticipates claim 18. But, in doing so, the Examiner ignores the four corners of that claim. For example, referring to Hanada's intermediate, the Examiner contends that "[t]he use of

[1] Even though this is not a *prima facie* case of anticipation, as explained below, Appellants submitted evidence on record to distinguish Hanada's teachings from the claims in order to speed prosecution.

trialkylphosphates is not a problem since applicant also teaches to use virus inactivation. . ." (Final Office Action at page 4.) However, whether or not the instant application teaches a method of virus inactivation during the process of making the solution is simply not relevant. Claim 18 is a composition claim, not a method claim. The relevant inquiry is whether Hanada's compositions contain the same set of ingredients and the same therapeutically suitable properties as the claimed compositions. The Examiner goes on to assert that claim 18 is anticipated because "Hanada [teaches] a therapeutic composition of thrombin." (*Id.* at page 5.) Again, the Examiner fails to consider that Hanada's "therapeutic composition of thrombin" does not contain a "noncovalently binding inhibitor of thrombin activity." Instead, it is a pure thrombin solution. Thus, the Examiner has not set forth on the record how Hanada could meet each and every element of claim 18, including the functional limitation. Therefore, this rejection is not a *prima facie* case of anticipation.

Finally, the only way Hanada's trialkylphosphate-containing solution could, *arguendo*, anticipate Appellants' claims is by inherency. A *prima facie* case of inherent anticipation requires substantial evidence or reasoning establishing that the Hanada solution, despite the presence of the trialkylphosphates, would be necessarily therapeutically suitable. *See In re Oelrich*, 666 F.2d 578,581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981); *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *see also* M.P.E.P. § 2131.01 (III). As the Federal Circuit has explained, "[i]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can*

Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1268-9, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991.) However, the Examiner has not provided such a showing here.

Because Hanada does not anticipate claim 18, it cannot anticipate any of claims 35-38. For all of the reasons above, the anticipation rejections over Hanada are not *prima facie* cases, and Appellants request the Board to overturn them.

3. Rejection of Claims 18 and 35-37 under 35 U.S.C. § 102(b): Allary or Lorne

The Examiner also asserts that claims 18 and 35-37 are anticipated by the English-language abstracts of Allary et al. ("Allary"; *Ann. Pharmaceutiques Francaises,* 48(3): 129-135 (1990)) or Lorne et al. ("Lorne"; *Rev. Fr. Transfus. Hemotiol.*, 32: 391-400 (1989)). (Appellants submitted the complete French-language articles in a previous Information Disclosure Statement and provide translations of relevant segments of those publications below.)

To support this rejection, the Examiner simply contends that the "references teach that benzamidine and thrombin are together in a composition" and that "[i]t is inherent that the references teach a thrombin with therapeutic activity." (Final Office Action at page 5.) Analyzing these remarks, it is clear again that the Examiner does not consider the four corners of claim 18. That claim requires a "thrombin preparation" containing both "thrombin" and a "noncovalently binding inhibitor of thrombin activity" in which the entire preparation with both ingredients is "suitable for therapeutic purposes," meaning that it can be directly administered to a patient. What the Examiner appears to contend is merely that Allary and Lorne's abstracts teach a composition including both thrombin and benzamidine and that Allary and Lorne's abstracts teach that thrombin is a

therapeutic protein. Thus, the Examiner has not considered that the entire preparation, with both ingredients, must be in a therapeutically suitable form in order to anticipate claim 18. Further, the Examiner does not cite any portion of the abstracts or explain how he reached these conclusions. Such unsupported, conclusory statements do not create a *prima facie* case of anticipation.

While this rejection is not a *prima facie* case, to speed prosecution, Appellants previously provided the examiner with a summary of the methods that these publications describe, and translations of relevant portions.[2] Review of the full documents shows that, like Hanada, neither Lorne nor Allary teaches a preparation comprising both "thrombin" and a "noncovalently binding inhibitor of thrombin activity" such that the overall composition with both ingredients is "suitable for therapeutic purposes." Instead, Allary and Lorne teach the use of a benzamidine inhibitor integrated into a solid SPHERODEX® matrix.[3] This solid matrix is used as a chromatography column to purify thrombin by affinity. Thus, an impure thrombin solution is poured over the solid benzamidine-containing column, which serves to separate thrombin from other ingredients. Therefore, the only way in which thrombin and benzamidine could come together according to Lorne and Allary is during this chromatography procedure. The Examiner has not explained how the mixtures in that chromatography procedure would necessarily and inherently be "suitable for therapeutic purposes." Further, Lorne specifically teaches that the thrombin obtained from the chromatography procedure is ***not*** therapeutically suitable because it must be further

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[2] Appellants are happy to provide complete translations upon request to assist the Board.

[3] The two publications appear to the undersigned to be cumulative, discussing the same affinity chromatography method.

purified by ultrafiltration or dialysis before it can be used. For example, Lorne at page 399, final full paragraph, may be translated as follows, referring to the modes of elution presented in Table 1 on page 398:

> Whatever mode of elution is chosen, the final recuperation of the thrombin obtained by chromatography must obligatorily be treated by a preliminary dialysis or ultrafiltration in 1 M NaCl to dissociate the complex formed with the elution agent. Afterwards, the salt can be eliminated by dialysis against water and 10 g/L glucose in order to obtain the protein in good condition for lyophilization.

Thus, there is no evidence that the eluates from either Lorne or Allary's columns are "suitable for therapeutic purposes" according to claim 18. Nor is there evidence that these eluates could inherently and necessarily produce the preparation of claim 18. For example, they may contain unsuitable run-off from the SPHERODEX® columns or unsuitable buffer ingredients. Further, there is no evidence that the thrombin solutions in the chromatography procedure are suitably sterilized.

In response to this illustration, the Examiner merely asked "why else would Allary and Lorne use the thrombin in a biological/fibrin glue unless it had therapeutic activity." (Final Office Action at page 5.) Again, such a question side-steps the four corners of claim 18. Claim 18 does not require only that thrombin be therapeutic, but that the entire claimed preparation, including the recited inhibitor, be "therapeutically suitable."

Thus, the Examiner has not raised a *prima facie* case of anticipation, and Appellants request the Board to overturn this rejection.

4. Rejection of Claim 38 under 35 U.S.C. § 103(a) over Hanada

As an alternative to the anticipation rejection of claim 38 over Hanada, the Examiner asserts that claim 38 is obvious over Hanada. This rejection suffers from the same deficiencies as the anticipation rejections discussed above in parts 2 and 3.

First, obviousness is to be analyzed according to the four factual inquiries of *Graham v. John Deere*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Thus, the Examiner must (a) determine the scope and contents of the prior art; (b) ascertain the differences between the prior art and the claims in issue; (c) resolve the level of ordinary skill in the pertinent art; and (d) evaluate evidence of secondary considerations. *Id.*, *and see* M.P.E.P. § 2141.

Second, in order for a combination of references to render a claim obvious, the references must teach or suggest every claim limitation. In addition, there must be both a suggestion or motivation to modify the references or to combine their teachings and a reasonable expectation of success in performing the combination. M.P.E.P. § 2142. Moreover, the motivation to combine the references and the reasonable expectation of success must both be found in the references themselves or in the knowledge generally available to one of ordinary skill in the art; not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); M.P.E.P. § 2142. The mere fact that the references ***can*** be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Instead, the modification or combination must be ***desirable***. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000).

An obviousness rejection must also be supported by substantial evidence and adequate scientific reasoning in accordance with *Zurko* and *In re Lee*, 277 F.3d 1338, 61 U.S.P.Q.2d 1430 (Fed, Cir. 2002). As the Federal Circuit made clear in *Lee*, "the factual analysis [of] whether to combine references must be thorough and searching. It must be based upon the objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." 61 U.S.P.Q.2d at 1433, citations omitted. Thus, the Office "cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies." *Id.* at 1435.

The Examiner supports this obviousness rejection with the same assertions used to support the section 102 rejection discussed in part 2 above. (Final Office Action at page 5.) As Appellants previously explained, those assertions are not based upon an analysis of the four corners of claim 18. Thus, they do not meet the substantial evidence requirements of *Zurko* and *Lee* and do not present a *prima facie* case of obviousness. In order to make a proper *prima facie* case, the Examiner must instead make "particular findings" based on the cited art, establishing "the reason the skilled artisan, with no knowledge of the claimed invention, would have selected *these components in the manner claimed.*" *Lee* at 1434, quoting *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) (emphasis added).

Further, as explained above, Hanada teaches making only a *pure thrombin* solution for eventual therapeutic use. Hanada does not suggest adding a thrombin inhibitor to that solution, but only teaches adding benzamidine as part of an intermediate trialkylphosphate treatment designed to kill viruses. (Hanada at col. 4, lines 13-37, and

col. 5, lines 25-50.) This treatment is performed before the thrombin is purified. (*Id.*) Hanada then teaches removing the components of the trialkylphosphate treatment, including any benzamidine, using a chromatography procedure such that only pure thrombin in a sodium citrate buffer remains. (*Id.*) It is only that final, pure thrombin solution that Hanada intends to use therapeutically. Thus, there is no motivation from Hanada alone to add a "noncovalent inhibitor of thrombin activity" to a thrombin solution such that the overall preparation is "suitable for therapeutic purposes" as claimed.

In fact, Hanada teaches away from adding such an inhibitor to a therapeutic thrombin solution by suggesting that the components of the viral inactivation step should be removed before any therapeutically useful preparation is made. (Hanada at col. 5, lines 25-50.) As the Federal Circuit points out, proceeding contrary to the accepted wisdom in the art is "strong evidence of unobviousness." *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986).

Further, even if Hanada's intermediate composition, discussed above, which contains both benzamidine and trialkylphosphates, could, *arguendo*, inherently anticipate claim 18, it still would not render claim 38 obvious. As the Federal Circuit explains, "the inherency of an advantage and its obviousness are entirely different questions. That which [is] inherent is not necessarily known. Obviousness cannot be predicated on that which is unknown." *In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 757. Thus, "[inherency] is quite immaterial if . . . one of ordinary skill in the art would not appreciate or recognize the inherent result." *In re Rijckaert*, 9 F.3d 1531, 1533, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993).

In addition, Hanada does not teach a thrombin solution containing benzamidine that meets the stability requirements of claim 38. Instead, Hanada is silent as to the stability of any thrombin solution, and the Examiner has not addressed this issue in the instant rejection.

For all of these reasons, the Examiner has not made a *prima facie* case of obviousness over Hanada. Further, there is no motivation to modify Hanada, and Hanada does not teach or suggest all of the limitations of claim 38. Thus, Appellants respectfully request the Board to overturn this rejection.

5. Rejection of Claims 18, 19, and 35-38 over Hanada, taken with Brezniak and Altshuler

The Examiner next rejects claims 18, 19, and 35-38 under § 103(a) over Hanada, taken with Brezniak et al. ("Brezniak"; *Blood Coagulation and Fibrinolysis*, 5: 847-8 (1994)) and Altshuler et al. ("Altshuler"; U.S. Patent No. 4,363,319). (Final Office Action at page 6.) As discussed in parts 2 and 4 above, Hanada does not anticipate any of Appellants' claims and teaches away from using thrombin inhibitors with thrombin in a formulation "suitable for therapeutic use."

Brezniak and Altshuler do not address the issue of thrombin inhibitors. Instead, the Examiner cites these publications for a teaching of using a soluble calcium salt, such as calcium chloride, as a stabilizer. Thus, neither publication cures the deficiencies of Hanada discussed above in parts 2 and 4.

In addition, as to calcium salts, Brezniak actually teaches away from the instant, claimed invention by suggesting that calcium chloride is not an effective thrombin stabilizer. For example, Brezniak, at page 847, in the first full paragraph of column 2,

states that thrombin was more active in sodium chloride than in calcium chloride, and that the "greater stability in NaCl must be attributed to increased thermal stability to denaturation." Similarly, the Examiner cited Altshuler at col. 2, lines 12-17, for a teaching of using calcium chloride as a stabilizer. But Altshuler's teaching is restricted to dry or powdered thrombin preparations. Altshuler comments that such dry or powdered preparations are not sufficiently stable in liquid form to be therapeutically useful. (Altshuler at col. 2, lines 17-39.) Thus, Altshuler's teachings are not transferable to liquid preparations such as that of claim 19.

For all of the reasons above, there no motivation to modify Hanada or combine Hanada with and Altshuler. In addition, as discussed in previous sections, the Examiner does not support his contentions with sufficient evidence or reasoning. Thus, Appellants respectfully request the Board to overturn this rejection.

6. Rejection of Claims 18, 19, and 35-38 under 35 U.S.C. § 103(a) over Two Combinations of Hanada, Lorne, Allary, Brezniak, and Altshuler

Finally, the Examiner rejects claims 18, 19, and 35-38 over combinations of all five of the above-cited publications. (Final Office Action at page 6.) First, the Examiner rejects the claims as allegedly unpatentable over the abstract of Allary or Lorne, taken with Hanada, Brezniak, and Altshuler. Second, the Examiner rejects the claims as allegedly unpatentable over Hanada, taken with the abstract of Allary or Lorne, and further with Brezniak and Altshuler. (*Id.*) Appellants address each of these rejections together, as they involve the same combination of publications.

These rejections suffer from the same deficiencies as the anticipation and obviousness rejections discussed in sections 2-5 above. The Examiner supports these

rejections with the same assertions used to support the section 102 rejections discussed in parts 2 and 3 above, which are not based upon an analysis of the four corners of claim 18. (Final Office Action at page 6.) Thus, they do not satisfy the requirements of *Zurko* and *Lee* and do not present a *prima facie* case of obviousness.

Moreover, Appellants have already explained that Hanada, Lorne, and Allary do not teach adding a "noncovalently binding inhibitor of thrombin activity" to a therapeutic thrombin solution. (See sections 2 and 3 above.) As stated in part 3 above, Lorne teaches specifically that once its column chromatography method is complete, it is obligatory to completely remove all ingredients of the chromatography buffers from the thrombin so as to obtain it in pure form. Only the pure thrombin solution obtained after this further purification is intended for therapeutic use. (Lorne at page 399, last full paragraph.) Similarly, Hanada teaches that the intermediate containing benzamidine must be further purified before any therapeutic solution of thrombin is prepared, and teaches only a pure thrombin solution for therapeutic use. (See parts 2 and 4-5 above.) Thus, none of these articles teach using a "noncovalently binding inhibitor of thrombin activity" in a therapeutically suitable solution. In fact, taken as a whole, Hanada, Lorne and Allary teach away from using thrombin inhibitors such as benzamidine. Again, Brezniak and Altshuler do not address this issue. Therefore, those two publications do not rescue the deficiencies of Hanada, Lorne, and Allary.

Thus, there is no motivation to combine these five publications, and Appellants respectfully request the Board to overturn these rejections.

IX. Conclusion

Appellants respectfully request the entry of this Appeal Brief. If any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of the Appeal Brief, such extension is hereby requested. If there are any required fees not enclosed herewith or otherwise accounted for, including any fees due under 37 C.F.R. §§ 1.16 or 1.17 or required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

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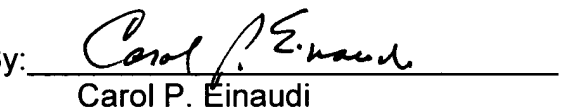
Dated: May 19, 2004

By: 
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Appendix

18. (Previously Presented) A thrombin preparation comprising thrombin and a noncovalently binding inhibitor of thrombin activity as stabilizer, wherein the thrombin preparation is suitable for therapeutic purposes.

19. (Previously Presented) The thrombin preparation as claimed in claim 18, which additionally comprises a soluble calcium salt, sodium chloride as stabilizer, a buffer substance, and further comprises at least one of

a sugar,

a sugar alcohol,

an amino acid,

a salt of a mono- or polycarboxylic acid, or

a salt of a mono- or polyhydroxycarboxylic acid,

wherein the thrombin preparation is stable in the liquid state.

35. (Previously Presented) The thrombin preparation of claim 18 wherein the noncovalently binding inhibitor of thrombin activity is benzamidine.

36. (Previously Presented) The thrombin preparation of claim 18 wherein the noncovalently binding inhibitor of thrombin activity is p-aminobenzamidine.

37. (Previously Presented) The thrombin preparation of claim 18 wherein, after 12 months of storage at 20-25 °C, the thrombin maintains at least 70% of its original level of activity.

38. (Previously Presented) The thrombin preparation of claim 18 wherein the thrombin preparation has a pH of from 5.0 to 8.0.